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Title

Characterization of bronchiectasis in the elderly

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ABSTRACT

Introduction. Although bronchiectasis particularly affects people ≥65 years of age, data describing clinical characteristics of the disease in this population are lacking. This study aimed at evaluating bronchiectasis features in older adults and elderly, along with their clinical outcomes.

Methods. This was a secondary analysis of six European databases of prospectively enrolled adult outpatients with bronchiectasis. Bronchiectasis characteristics were compared across three study groups: younger adults (18-65 years), older adults (66-75 years), and elderly (and ≥76 years). 3-year mortality was the primary study outcome.

Results. Among 1,258 patients enrolled (median age: 66 years; 42.5% males), 50.9% were ≥65 years and 19.1 ≥75 years old. Elderly patients were more comorbid, had worse quality of life and died more frequently than the others. Differences were detected among the three study groups with regard to neither the etiology nor the severity of bronchiectasis, nor the prevalence of chronic infection with *P. aeruginosa*. In multivariate regression model, age (OR: 1.05; p-value: <0.0001), low BMI (OR: 2.63; p-value: 0.02), previous hospitalizations (OR: 2.06; p-value: 0.006), and decreasing FEV_1 (OR: 1.02; p-value: 0.001) were independent predictors of 3-year mortality, after adjustment for covariates.

Conclusion. Bronchiectasis does not substantially differ across age groups. Poor outcomes in elderly patients with bronchiectasis might be directly related to individual's frailty that should be further investigated in clinical studies.

Keywords: frailty, cystic fibrosis, Pseudomonas, COPD, comorbidity

ABBREVIATION LIST

ABPA: Allergic Broncho-Pulmonary Aspergillosis

BMI: body mass index

BSI: Bronchiectasis Severity Index

BTS: British Thoracic Society

CCI: Charlson comorbidity index

CF: cystic fibrosis

CI: confidence intervals

COPD: Chronic Obstructive Pulmonary Disease

FEV_1: forced expiratory volume in the first second

GERD: Gastro-Esophageal Reflux Disease

HRCT: high-resolution computed tomography

IBD: inflammatory bowel disease

IQR: interquartile range

LTOT: long-term oxygen therapy

m-BSI: modified Bronchiectasis Severity Index

MRC: medical research council

MRSA: Methicillin-Resistant S. aureus

MSSA: Methicillin-Susceptible S. aureus

n: number

OR: odds ratios

SD: standard deviation

SGRQ: St. George's Respiratory Questionnaire

INTRODUCTION

Bronchiectasis is a chronic airway disease characterized by irreversibly damaged and dilated bronchi leading to recurrent episodes of respiratory infection [1]. Data from both United States of America (USA) and Europe have suggested that the clinical importance of bronchiectasis is rising reflecting an increase in prevalence, hospital admissions and mortality [2.3].

Much of our knowledge on the management and treatment of bronchiectasis is based on cystic fibrosis (CF), mainly recognized as a disease of children and young adults. In contrast, analyses from administrative databases highlighted that bronchiectasis predominantly affects elderly people increasing mortality of approximately 3% per year and causing a high economic burden on healthcare systems [3,4].

Management of many diseases in the elderly is more complex than in younger patients due to the impact of several age-related conditions, including comorbidities, cognitive impairment, and frailty, all of which can independently affect adherence to poly-pharmacological regimens, follow-up visits, hospitalizations, and the patient's overall survival [5]. Despite the recognition that bronchiectasis seems to occur most commonly in the elderly, there are no large-scale studies characterizing the extent to which age impacts clinical features and outcomes of this disease.

The aim of this study was to evaluate clinical, radiological, microbiological, and functional characteristics, along with the severity of the disease and clinical outcomes, in adults and elderly patients with bronchiectasis.

MATERIALS AND METHODS

Study population

This study is part of the FRIENDS (Facilitating Research Into Existing National DataSet) project aimed to foster collaboration within the EMBARC network [6]. It was a secondary analysis of six databases of prospectively enrolled outpatients with bronchiectasis referred to the bronchiectasis clinics of university teaching hospitals in Monza (Italy), Dundee (UK), Leuven (Belgium), Athens (Greece), Sremska Kamenica (Serbia) and Galway (Ireland) between 2009 and 2014. Consecutive patients aged ≥18 years with a diagnosis of bronchiectasis on high-resolution computed tomography (HRCT) scan in stable state were enrolled. Patients with cystic fibrosis or traction bronchiectasis due to pulmonary fibrosis were excluded. A further exclusion criterion for the Leuven cohort was the presence of active cancer. Collection of selected variables was approved at each individual centre by the local ethical committee or institutional review board.

Data collection

At the time of baseline assessment, all patients were clinically stable and underwent the same comprehensive diagnostic work-up in each site according to the 2010 British Thoracic Society (BTS) guidelines [7]. Demographics, comorbidity, severity of the disease, etiology of bronchiectasis, respiratory symptoms, sputum evaluation, radiological, functional, and laboratory findings during clinical stability, quality of life and outcomes during a three-year follow-up period were uniformly recorded in each local database. Process to define the etiology of bronchiectasis is reported in the supplementary material.

The Charlson comorbidity index (CCI) was used to assess comorbidity; this is a sum score of 19 weighted diseases with higher scores denoting increasing burden of comorbidity [8]. COPD was defined according to the GOLD initiative [9]. The severity of bronchiectasis was evaluated according to the Bronchiectasis Severity Index (BSI) [10]. In addition, in some analyses comparing

different age groups, a modified BSI (m-BSI), calculated without including age as a factor, was used. Radiological severity of bronchiectasis was assessed using a modified Reiff score, which rates the number of involved lobes (with the lingula considered to be a separate lobe) and the degree of dilatation (range: 1-18) [10]. Each participating center performed standardized etiological testing recommended by the BTS guidelines [7]. St. George's Respiratory Questionnaire was administered to measure patients' quality of life [11]. Chronic infection was defined by the isolation of potentially pathogenic bacteria in sputum culture on two or more occasions, at least 3 months apart over a 1-year period [12]. The predominant pathogen was the organism grown most frequently over the study period. Patients who were unable to provide sputum samples due to absence of a productive cough were classified as not having a chronic infection for the purposes of analysis as previously described.

Study groups and outcomes

The cohort was split into three groups based on age at enrolment: 18-65 years (younger adults), 66-75 years (older adults), and 76 years or over (elderly). The primary outcome was all-cause mortality at three-year follow-up. Exacerbations and hospitalizations were secondary outcomes (see supplementary material).

Statistical analysis

All statistical analyses were run using Stata® 13 (StataCorp, College Station, TX, USA). Categorical data are presented as absolute number (n) and percentage (%). Normally distributed data are shown as mean with standard deviation (SD), whereas non-normally distributed data are presented as median with interquartile range (IQR). The chi-squared test and Mann Whitney U test were used for comparison of categorical and non-parametric numerical data, respectively. For comparisons of more than two groups, one-way analysis of variance or the Kruskal-Wallis test

were used as appropriate. The association between 3-year mortality and collected variables was evaluated using uni- and multi-variate logistic regressions reporting odds ratios (OR) and 95% confidence intervals [CI]. Age and m-BSI scores were divided in tertiles, while CCI score was dichotomized (*i.e.*, $\leq$1 vs. $\geq$2), according to their distribution. The covariates were chosen with *a priori*-selection based on previous research and clinical rationale (i.e., independent association with mortality in elderly patients with respiratory diseases). The calculated p-values were two-tailed, with values less than 0.05 considered statistically significant.

RESULTS

Study sample

A total of 1,258 patients were enrolled within the six centers (median [IQR] age: 66 [56-74] years; 42.5% males): 286 patients in Dundee, 280 in Galway, 230 in Monza, 190 in Leuven, 159 in Athens, and 113 in Sremska Kamenica, see Table A (supplementary material). Distribution of patients according to age is depicted in Figure 1 with a range from 18 to 94 years. Among the entire study sample, 618 patients (49%) were younger adults, 400 (32%) older adults, and 240 (19%) were elderly. Among this last group, 34 patients (2.7%) patients were 85 years of age or older.

Demographics, clinical, functional and radiological status, microbiology, severity of the disease, quality of life, and long-term treatment of the three age groups are presented in Table 1. A significantly higher prevalence of males and smoker/ex-smokers, a worse radiological impairment and pulmonary function status, higher comorbidity prevalence, and a worse quality of life were detected in older adults and elderly patients in comparison to younger adults. The global severity of bronchiectasis evaluated with the m-BSI was not different among the age groups. Younger adults, older adults, and elderly patients showed no significant differences in terms of clinical symptoms related to bronchiectasis, including daily cough, daily sputum and haemoptysis, nor systemic inflammation during stable state.

The most common etiologies of bronchiectasis were post-infective (25%), COPD-related (13%), connective tissue disease-related (7.1%), and immunodeficiency (4.5%), while bronchiectasis was idiopathic in 36% of the patients. While bronchiectasis related to asthma, inflammatory bowel disease (IBD), and ciliary dysfunction were more prevalent in younger adults, COPD-related bronchiectasis was more prevalent in older adults and elderly patients, see Table 2. No other significant differences in terms of prevalence of the etiologies were detected when the three study groups were compared.

Microbiology

Microbiology and long-term antibiotic therapy are reported in Table 3. No significant differences among age groups were detected with regard to chronic infection with *Pseudomonas aeruginosa*. The only significant differences in terms of prevalence of chronic infection among the different age groups were detected for *Haemophilus influenzae* (more prevalent in younger adults), *Streptococcus pneumoniae* (more prevalent in younger adults), and *Enterobacteriaceae* (more prevalent in older adults and elderly patients).

Study outcomes

Data on outcomes were not available for 37 patients at 1-year and for 219 patients at 2 and 3-year follow up. Among the entire sample, during the first year of follow up the median (IQR) number of exacerbations was 1 (0-2), and 221 patients (19%) experienced at least one severe exacerbation requiring hospitalization. Mortality was 3.4% at one year, 6.6% at two years, and 11% at three years. Prevalence of study outcomes in the three age groups is shown in Table 4.

The logistic regression analysis, adjusted for several confounders including centers, highlighted the role of age (OR: 1.05; p-value: <0.0001), low BMI (OR: 2.63; p-value: 0.02), previous hospitalizations (OR: 2.06; p-value: 0.006), and decreasing FEV_1 (OR: 1.02; p-value: 0.001) as independent predictors of 3-year mortality in the entire cohort.

DISCUSSION

Our study shows that among bronchiectasis patients referring to six European tertiary care centers, more than 50% are over 65 years with almost one out of five greater than 75 years of age. Predictably, oldest patients have an increased comorbidity level, experience a worse quality of life and die more frequently during a 3-year follow-up in comparison to younger adults. However, bronchiectasis severity, signs and symptoms of the disease, systemic inflammation and chronic infection with *P. aeruginosa* did not different among older adults, elderly and younger adults.

Little information is available across Europe regarding the prevalence of bronchiectasis in older people. According to data provided by the German Federal Insurance Authority, individuals aged 75 years or more have the highest prevalence of bronchiectasis, up to 228 and 200 per 100,000 population in men and women, respectively [13]. By confirming high bronchiectasis prevalence in older adults and elderly people, our data represent a significant step forward in this field since we collated data from multicenter, observational cohorts of consecutively enrolled patients from several countries. We decided to identify three age groups because elderly represents a very heterogeneous group of patients. According to several studies, the cut-off of 65 years is not representative of the biological complexity of the whole elderly population. Therefore, we decided to stratify people over 65 years of age into two more groups in order to appreciate several differences in clinical characteristics and outcomes.

Western countries are experiencing an “ageing population” with older people representing the fastest growing section of the whole population; hence, it is imperative to try to understand the mechanisms regulating the interaction among different diseases in these individuals. The high comorbidity burden that characterizes our cohort represents the substrate for an increased risk of disability and frailty in older subjects [14]. Furthermore, it represents the clinical background for a frequent use of health care services and for a worse quality of life for elderly patients [15,16].

We found that age is an independent predictor of 3-year mortality, in line with previously published literature [10]. Increasing age was associated with an increased mortality risk (hazard ratio: 1.045) in a prospective study carried out in Belgium and in a cohort study in the UK (relative risk: 1.10) [17,18]. The role of age may be explained with an increased risk of reduced biological reserve occurring with age and comorbidity. Indeed, age is an important risk factor for frailty [19]. Frailty represents a state of increased vulnerability related to a poor level of homeostasis after a stressful event, with a corresponding increased risk of adverse outcomes [19]. Several studies showed that frailty is a much more powerful predictor of poor outcomes than age, indirectly suggesting that if frailty is taken into account in the pathophysiological relationship with mortality, age could weaken its importance [20,22]. Future studies in older people with bronchiectasis should, therefore, consider frailty as a crucial factor and record variables such as weakness, low gait speed, poor endurance, and cognitive impairment.

At least three important findings of the present study may contribute to expand our knowledge on bronchiectasis. First, no significant differences seem to exist in etiologies of bronchiectasis among younger adults, older adults and elderly, except for COPD-associated bronchiectasis, which was most common in the elderly, and bronchiectasis associated to ciliary dysfunctions, asthma or IBD, which was most common among younger adults. Second, we found that variables specifically related to bronchiectasis showed similar frequencies across all age groups. In particular, signs and symptoms of bronchiectasis, the level of systemic inflammation, and exacerbation rates during follow-up did not significantly vary among the three age groups. Third, we identified similar prevalence of pathogens leading to chronic infections among the selected age groups, with the only exceptions of *S. pneumoniae* and *H. influenzae* which were most prevalent among the younger adults and *Enterobacteriaceae* which was most prevalent in the elderly group.

Notably, prevalence of chronic infection with *P. aeruginosa* was not different by age. The presence of *P. aeruginosa* in bronchiectasis patients clearly defines a specific clinical phenotype and leads to

worse clinical outcomes [23-25]. Our study suggests that age by itself might not represent a specific factor for the acquisition of *P. aeruginosa* and we can speculate that exposure to different infections may be the result of different lifestyles and/or comorbidity. Furthermore, chronic infection with *P. aeruginosa* was not a predictor of 3-year mortality in our cohort. We could speculate that predisposing factors of vulnerability towards potential stressors (*i.e.,* the reduced biological reserve occurring with age) are as important, if not more, than the precipitating factors (*i.e.*, the bacterial virulence). It seems reasonable to think that it is the interaction between *P. aeruginosa* and the host, more than the sole presence of the pathogen that might affect a patient's biological reserve. The biological reserve is the final result of the number, type, severity and interaction of different diseases. Chronic infection with *P. aeruginosa* might accelerate the decline of each individual's biological reserve, leading to a poor quality of life and worse outcomes. This represents a crucial field for future research that should be focused on: a) the understanding of specific risk factors for acquiring chronic infection with *P. aeruginosa*, b) the evaluation of mechanisms of interaction between *P. aeruginosa* and the bronchiectatic host; c) the identification of biomarkers expressing this interaction; d) and, finally, the development of therapeutic strategies to interrupt the vicious cycle of *P. aeruginosa* decreasing patient's biological reserve to the point of death.

Results of our study might have other important implications. From a research perspective, a complete analysis of the number, type, severity and interaction of various diseases in bronchiectasis is urgently needed. From a clinical perspective, our results clearly indicate the need for pulmonologists taking care of patients with bronchiectasis to acquire specific geriatric competencies or, at least, create the premises for collaborating with physician experts in ageing and long-term care [14]. Among these competencies, the acquisition of geriatric methods to assess a patient's comorbidity and frailty should be a priority [26]. Furthermore, a special

attention should be given to possible interactions between bronchiectasis therapies, such as long-term azithromycin, and other drugs elderly patients usually take for other diseases.

One of the limitations of this study is the inclusion of patients coming from tertiary care centers and the presence of missing data on 2- and 3-year mortality for 17% of our patients. Thus, the prevalence of older adults and elderly people with bronchiectasis might be underestimated if there is referral bias favoring younger adults. Another important limitation is the absence of data on causes of death that could help to differentiate between those patients who died "with" bronchiectasis and those who died "because of" bronchiectasis. This difference between bronchiectasis-related *versus* all-cause mortality is crucial especially in elderly patients and should be collected in future studies focused on this topic. Furthermore, patients' frailty and functional *status* would be important to understand the relationship between age and mortality in this patient population. Finally, we did not evaluate the potential interactions between bronchiectasis and specific diseases which may unveil clusters of comorbidity playing a relevant role in determining poor quality of life and increased mortality.

This is the largest cohort of outpatients with bronchiectasis published in the literature so far incorporating patients from six European countries. Furthermore, patients' enrolment is equally balanced among different centers.

CONCLUSIONS

This large European study confirms that among patients with bronchiectasis more than 50% are elderly and very elderly. In light of the absence of substantial differences in terms of bronchiectasis characteristics across age groups, other factors, possibly related to individual's frailty and vulnerability, might explain the increased rate of mortality we found in older patients. We strongly suggest that future research should be focused on individual's determinants of frailty with the aim to assess possible interactions with bronchiectasis and potential relationship with the outcomes.

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REFERENCES

[1] Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. Eur Respir J 2015;45(5):1446-1462.

[2] Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. Eur Respir J 2016;47(1):186-193.

[3] Seitz AE, Olivier KN, Steiner CA, Montes de Oca R, Holland SM, Prevots DR. Trends and burden of bronchiectasis associated hospitalizations in the United States, 1993-2006. Chest 2010;138(4):944-949.

[4] Roberts HJ, Hubbard R. Trends in bronchiectasis mortality in England and Wales. Respir Med 2010;104(7):981-985.

[5] Kane RL, Priester R, Totten AM. Meeting the Challenge of Chronic Illness. The Johns Hopkins University Press, Baltimore; 2005: 3-42.

[6] Chalmers JD, Aliberti S, Polverino E, Vendrell M, Crichton M, Loebinger M et al. The EMBARC European Bronchiectasis Registry: protocol for an international observational study. ERJ Open Res 2015;1: 00081-2015

[7] Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010;65:Suppl.1,i1–i58.

[8] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–383.

[9] Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of COPD. http://www.goldcopd.org/uploads/users/files/

GOLD_Report_2014_Jun11.pdf.

[10] Chalmers JD, Goeminne P, Aliberti S, McDonnell MJ, Lonni S, Davidson J et al. The bronchiectasis severity index. An international derivation and validation study. Am J Respir Crit Care Med 2014;189(5):576-585.

[11] Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. Am J Respir Crit Care Med 1997;156:536–541.

[12] Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med 2000;162:1277–1284.

[13] Ringshausen FC, de Roux A, Diel R, Hohmann D, Welte T, Rademacher J. Bronchiectasis in Germany: a population-based estimation of disease prevalence. Eur Respir J 2015;46(6):1805-1807.

[14] Bellelli G, Aliberti S. Is it time for a "pneumo-geriatrician" for frail old patients with respiratory diseases? Eur J Intern Med 2014;25(4):303.

[15] Anderson G. Chronic care: making the case for ongoing care. Princeton, NJ: Robert Wood Johnson Foundation; 2010.

[16] Sundh J, Johansson G, Larsson K, Lindén A, Löfdahl CG, Janson C et al. Comorbidity and health-related quality of life in patients with severe chronic obstructive pulmonary disease attending Swedish secondary care units. Int J Chron Obstruct Pulmon Dis 2015;10:173-183.

[17] Goeminne PC, Nawrot TS, Ruttens D, Seys S, Dupont LJ. Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. Respir Med. 2014;108(2):287-96.

[18] Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. Eur Respir J. 2009 Oct;34(4):843-9.

[19] Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet

2013;381(9868):752-762.

[20] Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-156.

[21] Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hébert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. Lancet 1999;353(9148):205-206.

[22] Buurman BM, Hoogerduijn JG, de Haan RJ, Abu-Hanna A, Lagaay AM, Verhaar HJ et al. Geriatric conditions in acutely hospitalized older patients: prevalence and one-year survival and functional decline. PLoS One 2011;6(11):e26951.

[23] Aliberti S, Lonni S, Dore S, McDonnell MJ, Goeminne PC, Dimakou K et al. Clinical phenotypes in adult patients with bronchiectasis. Eur Respir J In press. doi: 10.1183/13993003.01899-2015.

[24] Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonization on Prognosis in Adult Bronchiectasis. Ann Am Thorac Soc 2015;12(11):1602-1611.

[25] McDonnell MJ, Jary HR, Perry A, MacFarlane JG, Hester KL, Small T et al. Non cystic fibrosis bronchiectasis: A longitudinal retrospective observational cohort study of Pseudomonas persistence and resistance. Respir Med 2015;109(6):716-726.

[26] Arora VM, Johnson M, Olson J, Podrazik PM, Levine S, Dubeau CE et al. Using assessing care of vulnerable elders quality indicators to measure quality of hospital care for vulnerable elders. J Am Geriatr Soc 2007;55(11):1705-1711.

FIGURE LEGEND

Figure 1. Distribution of patients according to age.

TABLES

Table 1. Demographic, clinical and epidemiological patients' characteristics stratified according to age

Variable	Indicator	18-65 years (Younger adults) (n= 618)	66-75 years (Older adults) (n= 400)	≥76 years (Elderly) (n= 240)	p-value
Demographics					
Age, years	median (IQR)	56 (46-61)	71 (68-73)	80 (78-82)	0.0001[a, b, c]
Male	n (%)	232 (38)	174 (44)	129 (54)	<0.0001[b, c]
Underweight	n (%)	43 (7.3)	27 (7)	15 (6.6)	0.94
Either smokers or ex-smokers	n (%)	233 (38)	169 (42)	116 (48)	0.015[b]
Severity of the disease					
BSI score	median (IQR)	4 (3-9)	7 (5-11)	9 (7-13)	0.0001[a, b, c]
Modified BSI[#]	median (IQR)	3 (1-7)	3 (1-8)	4 (2-8)	0.072
Radiological Status					
Reiff score	Mean (SD)	4.2 (2.9)	4.9 (3.3)	5.1 (3.1)	<0.001[a, b]
Comorbidity					
Charlson Comorbidity Index>1	n (%)	154 (25)	159 (40)	126 (53)	<0.0001[a, b]
COPD	n (%)	86 (14)	86 (22)	77 (32)	<0.0001[c]
Diabetes mellitus	n (%)	47 (7.6)	56 (14)	31 (13)	0.002[a]

Chronic renal failure	n (%)	30 (4.9)	23 (5.8)	34 (14)	<0.0001[b, c]
Chronic heart failure	n (%)	49 (7.9)	57 (14)	40 (17)	<0.0001[a, b]
Previous acute myocardial infarction	n (%)	34 (5.5)	49 (12)	45 (19)	<0.0001[a, b]
Mild liver disease	n (%)	9 (1.5)	6 (1.5)	3 (1.3)	0.97
Moderate-to-severe liver disease	n (%)	7 (1.1)	6 (1.5)	3 (1.3)	0.88
Previous cerebro-vascular accident	n (%)	20 (3.2)	23 (5.8)	22 (9.2)	0.002[b]
Peripheral vascular disease	n (%)	37 (6.0)	26 (6.5)	43 (18)	<0.0001[b, c]
Dementia	n.(%)	1 (0.2)	5 (1.3)	8 (3.3)	<0.0001[b]
Rheumatologic disease	n (%)	50 (8.1)	49 (12)	21 (8.8)	0.08
Peptic ulcer disease	n (%)	28 (4.5)	31 (7.8)	20 (8.3)	0.04[a, b]
Solid tumor	n (%)	27 (4.4)	48 (12)	25 (10)	<0.0001[a, b]
Leukemia	n (%)	4 (0.7)	9 (2.3)	1 (0.4)	0.03[a]
Lymphoma	n (%)	1 (0.2)	3 (0.8)	3 (1.3)	0.13
HIV infection	n (%)	2 (0.3)	0 (0)	0 (0)	0.69
Clinical, laboratory and functional status					
Daily cough	n (%)	457 (74)	291 (73)	175 (73)	0.90
Daily sputum	n (%)	357 (58)	255 (64)	144 (60)	0.16
Prior history of haemoptysis	n (%)	102 (17)	77 (19)	39 (16)	0.47
MRC class IV and V	n (%)	91 (17)	94 (26)	62 (27)	<0.0001[a, b]
LTOT	n (%)	39 (6.3)	39 (9.8)	20 (8.3)	0.13
FEV_1, % predicted	median	78 (57-96)	75 (53-94)	67 (51-84)	0.0002[b, c]

	(IQR)				
C-reactive protein, mg/L	median (IQR)	5 (2-9)	5 (3-10)	6 (3-12)	0.10
Quality of life					
SGRQ	median (IQR)	36.1 (24.5-51.5)	38.9 (26.4-59.6)	50.8 (32.3-63.3)	0.007[b]

n: number; IQR: interquartile range; BSI: Bronchiectasis Severity Index; MRC: medical research council; LTOT: long-term oxygen therapy. SGRQ: St. George's Respiratory Questionnaire; FEV-1: forced expiratory volume in the first second; [a]p-value<0.017 younger adults vs. older adults; [b]p-value<0.017 younger asults vs. elderly; [c]p-value<0.017 older adults vs. elderly.

Table 2. Etiology of bronchiectasis in the three study groups.

Disease	Indicator	18-65 years (Younger adults) (n= 618)	66-75 years (Older adults) (n= 400)	≥76 years (Elderly) (n= 240)	p-value
Idiopathic	n (%)	211 (34)	156 (39)	88 (37)	0.29
Post-infective	n (%)	154 (25)	104 (26)	51 (21)	0.39
COPD	n (%)	50 (8.1)	51 (13)	57 (24)	<0.0001[a, b, c]
Connective tissue disease	n (%)	41 (6.6)	32 (8.0)	16 (6.7)	0.68
Immunodeficiency	n (%)	31 (5.0)	18 (4.5)	8 (3.3)	0.57
ABPA	n (%)	30 (4.9)	15 (3.8)	9 (3.8)	0.63
Asthma	n (%)	29 (4.7)	8 (2.0)	4 (1.7)	0.02[a, b]
Inflammatory bowel disease	n (%)	18 (2.9)	4 (1.0)	2 (0.8)	0.04
Ciliary dysfunction	n (%)	19 (3.1)	1 (0.3)	0 (0)	<0.0001[a, b]
Aspiration/GERD	n (%)	7 (1.1)	4 (1.0)	3 (1.3)	0.96
Alpha-1 antitrypsin deficiency	n (%)	10 (1.6)	2 (0.5)	0 (0)	0.06
Congenital	n (%)	5 (0.8)	0 (0)	0 (0)	0.07
Obstructive (lung carcinoid)	n (%)	1 (0.2)	0 (0)	0 (0)	0.60
Other	n (%)	11 (1.8)	5 (1.3)	3 (1.3)	0.83

COPD: Chronic Obstructive Pulmonary Disease; ABPA: Allergic Broncho-Pulmonary Aspergillosis; GERD: Gastro-Esophageal Reflux Disease; [a]p-value<0.017 younger adults vs. older adults; [b]p-value<0.017 younger asults vs. elderly; [c]p-value<0.017 older adults vs. elderly.

Table 3. Microbiology and long-term antibiotic treatment in the entire study population and in different sub-groups.

Variables	Indicator	18-65 years (Younger adults) (n= 618)	66-75 years (Older adults) (n= 400)	≥76 years (Elderly) (n= 240)	p-value
Patients with chronic infection	n (%)	229 (37)	147 (37)	80 (33)	0.58
Chronic infection with					
P. aeruginosa	n (%)	83 (13)	62 (16)	36 (15)	0.63
H. influenzae	n (%)	113 (18)	51 (13)	21 (8.8)	0.001[b]
S. aureus	n (%)	43 (7)	25 (6.3)	14 (5.8)	0.81
MRSA	n (%)	10 (1.6)	7 (1.8)	4 (1.7)	1.00
MSSA	n (%)	33 (5.3)	18 (4.5)	10 (4.2)	0.72
S. pneumoniae	n (%)	33 (5.3)	11 (2.8)	3 (1.3)	0.007[b]
M. catarrhalis	n (%)	30 (4.9)	13 (3.3)	7 (2.9)	0.29
Enterobacteriaceae	n (%)	19 (3.1)	24 (6.0)	19 (7.9)	0.006[b]
K. pneumoniae	n (%)	6 (1.0)	3 (0.8)	4 (1.7)	0.54
E. coli	n (%)	4 (0.7)	6 (1.5)	4 (1.7)	0.23
Proteus spp.	n (%)	1 (0.2)	3 (0.8)	1 (0.4)	0.34
A. fumigatus	n (%)	2 (0.3)	1 (0.3)	1 (0.4)	1.00
Others	n (%)	6 (1)	16 (4)	6 (2.5)	0.01[a]

n: number; *p among the three groups; MRSA: Methicillin-Resistant *S. aureus*; MSSA: Methicillin-Susceptible *S. aureus*; [a]p-value<0.017 younger adults vs. older adults; [b]p-value<0.017 younger asults vs. elderly; [c]p-value<0.017 older adults vs. elderly.

Table 4. Follow-up data among the three study groups.

Variables	Indicator	18-65 years (Younger adults) (n= 618)	66-75 years (Older adults) (n= 400)	≥76 years (Elderly) (n= 240)	p-value
≥2 exacerbations in 1-year follow up	n.(%)	266 (43)	170 (43)	96 (40)	0.70
≥3 exacerbations in 1-year follow up	n.(%)	105 (18)	78 (21)	39 (17)	0.39
≥1 hospitalization in 1-year follow up	n.(%)	100 (17)	62 (17)	59 (26)	0.005[b, c]
Mortality in 1-year follow up	n.(%)	12 (2.0)	12 (3.1)	18 (7.9)	<0.0001[b, c]
Mortality in 2-year follow up	n.(%)	21 (3.9)	23 (7.5)	25 (13)	<0.0001[a, b]
Mortality in 3-year follow up	n.(%)	31 (5.8)	39 (13)	41 (21)	<0.0001[a, b, c]

[a]p-value<0.017 younger adults vs. older adults; [b]p-value<0.017 younger asults vs. elderly; [c]p-value<0.017 older adults vs. elderly.

Table 5. Logistic regression analysis to assess the relationship between mortality in 3-year follow up and epidemiological, clinical, and demographic variables in the entire cohort (N=1,039)

Mortality in 3-year follow up (entire cohort)				
Variables	**Univariate**		**Multivariate**	
	Odds Ratio (IC 95%)	**p-value**	**Odds Ratio (IC 95%)**	**p-value**
Age, years	1.06 (1.04-1.08)	<0.0001	1.05 (1.03-1.08)	<0.0001
Male	2.69 (1.78-4.05)	<0.0001	1.53 (0.92-2.54)	0.10
Underweight	3.19 (1.71-5.95)	<0.0001	2.63 (1.20-5.75)	0.02
Smokers/Ex-smokers	2.85 (1.89-4.28)	<0.0001	1.22 (0.69-2.17)	0.50
Reiff score	2.35 (1.50-3.68)	<0.0001	0.98 (0.57-1.69)	0.95
Daily cough	0.85 (0.54-1.33)	0.47		
Daily sputum	0.80 (0.54-1.19)	0.27		
Prior history of haemoptysis	0.83 (0.47-1.47)	0.52		
MRC class IV and V	3.71 (2.46-5.60)	<0.0001	1.39 (0.82-2.35)	0.23
Exacerbations in the previous year	1.10 (1.00-1.22)	0.06		
≥1 hospitalization in the previous year	2.69 (1.80-4.01)	<0.0001	2.06 (1.23-3.46)	0.006
Decreasing FEV_1, % predicted	1.04 (1.03-1.05)	<0.0001	1.02 (1.01-1.03)	0.001
Individuals with a bacterial colonization	1.05 (0.70-1.57)	0.81		
P. aeruginosa infection	1.84 (1.14-2.96)	0.012	1.33 (0.71-2.50)	0.37
Individuals with ≥ 2 bacterial colonizations	0.98 (0.55-1.74)	0.94		

Bacterial infection than *P. aeruginosa infection*	0.62 (0.37-1.03)	0.07		
Previous cerebro-vascular accident	1.67 (0.82-3.38)	0.16		
Dementia	6.21 (1.94-19.90)	0.002	1.80 (0.48-6.69)	0.38
COPD	4.23 (2.80-6.41)	<0.0001	1.52 (0.81-2.83)	0.19
Rheumatologic disease	1.51 (0.84-2.72)	0.17		
Hematological malignancy	1.40 (0.41-4.85)	0.59		
Moderate-to-severe liver disease	1.26 (0.37-4.31)	0.71		
Diabetes mellitus-related organ damage	0.48 (0.11-2.04)	0.32		
Leukemia	1.53 (0.33-6.99)	0.58		
Lymphoma	1.40 (0.17-11.71)	0.76		
ABPA	0.52 (0.16-1.70)	0.28		
Aspiration/GERD	1.40 (0.31-6.34)	0.66		
Asthma	0.75 (0.23-2.50)	0.64		
Connective tissue disease	1.27 (0.65-2.47)	0.48		
Inflammatory bowel disease	1.20 (0.27-5.34)	0.81		
Immunodeficiency	0.95 (0.37-2.44)	0.91		
Post-infective etiology	0.74 (0.45-1.20)	0.22		
Long-term macrolide and/or inhaled antibiotic treatment	1.13 (0.75-1.69)	0.55		
Long-term macrolide treatment	0.95 (0.63-1.45)	0.82		

MRC: medical research council; FEV_1: forced expiratory volume in the first second; COPD: Chronic Obstructive Pulmonary Disease; BMI: body mass index.